A Randomized, Open-label (formerly Double-Blind), Phase 2 Trial to Assess Safety and Efficacy of Lenvatinib at Two Different Starting Doses (18 mg vs. 14 mg QD) in Combination with Everolimus (5 mg QD) in Renal Cell Carcinoma Following One Prior VEGF-Targeted Treatment

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Primary ObjectiveTo assess whether a starting dose of lenvatinib 14 mg in combination with everolimus 5 mg once daily (QD) will provide comparable efficacy (based on objective response rate [ORR] at 24 weeks [ORR24W]) with an improved safety profile...

Ethical review	Approved WMO
Status	Completed
Health condition type	Renal and urinary tract neoplasms malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON50669

Source
ToetsingOnline

Brief title
E7080-G000-218

Condition

- Renal and urinary tract neoplasms malignant and unspecified
- Renal disorders (excl nephropathies)

Synonym
Renal Cell Carcinoma ; renal-cell cancer

Research involving
Human

Sponsors and support

Primary sponsor: Eisai
Source(s) of monetary or material Support: Eisai Ltd.

Intervention

Keyword: Everolimus, Lenvatinib, Renal Cell Carcinoma

Outcome measures

Primary outcome

Primary Endpoints

• Objective response rate (ORR) at Week 24 (ORR24W) as assessed by the investigator according to RECIST 1.1. ORR24W is defined as the proportion of subjects with best overall response (BOR) of complete response (CR) or partial response (PR) at the Week¬24 (after randomization) time point or earlier. To be considered a BOR, all responses must be confirmed no less than 4 weeks after the initial assessment of response.

• Proportion of subjects with intolerable Grade 2 and any >= Grade 3 TEAEs within 24 weeks after randomization (as of the Week-24 time point).

Secondary outcome

Secondary Endpoints

• Progression-free survival (PFS), defined as the time from the date of randomization to the date of first documentation of disease progression or date

of death, whichever occurs first. PFS censoring rules will be defined in the statistical analysis plan (SAP) and will follow FDA guidance.

• ORR as assessed by the investigator according to RECIST 1.1 at the end of treatment. ORR is defined as the proportion of subjects with BOR of CR or PR at the end of treatment. To be considered BOR, all responses must be confirmed no less than 4 weeks after the initial assessment of response.

• Overall safety profile and tolerability of lenvatinib in combination with everolimus.

• Proportion of subjects who discontinue treatment due to toxicity, defined as the proportion of subjects who discontinue study treatment due to TEAEs.

• Time to treatment failure due to toxicity, defined as the time from the date of randomization to the date that a subject discontinues study treatment due to TEAEs.

• Lenvatinib and everolimus exposure parameters and PK and PD drug-drug interactions.

• Overall survival (OS), measured from the date of randomization until date of death from any cause. In the absence of confirmation of death, subjects will be censored either at the date that the subject was last known to be alive or

the date of data cutoff, whichever comes earlier.

• Health-Related Quality of Life (HRQoL) will be assessed using the Functional Assessment of Cancer Therapy Kidney Syndrome Index-Disease-Related Symptoms (FKSI-DRS), the European Organization for the Research and Treatment of Cancer (EORTC) QLQ-C30 and the European Quality of Life (EuroQol) EQ-5D-3L instruments.

• PFS2, defined as the time from randomization to the date of disease progression after next line of therapy or death from any cause, whichever occurs first. PFS2 censoring rules will be defined in the SAP.

Study description

Background summary

This is a multicenter, randomized, open-label study conducted as a postmarketing requirement by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to evaluate an alternate dose regimen for lenvatinib in combination with everolimus. In subjects with advanced renal cell carcinoma (RCC) following one prior anti-angiogenic treatment, the current approved lenvatinib dose is 18 mg daily in combination with everolimus 5 mg daily.
This study will evaluate the combination of lenvatinib and everolimus in subjects with advanced predominant clear cell RCC following one prior vascular endothelial growth factor (VEGF)-targeted treatment at 14-mg starting dose of lenvatinib and allow up-titration of lenvatinib to determine whether this regimen provides comparable efficacy but has a better safety profile than the 18 mg starting dose.

Study objective

Primary Objective
To assess whether a starting dose of lenvatinib 14 mg in combination with everolimus 5 mg once daily (QD) will provide comparable efficacy (based on objective response rate [ORR] at 24 weeks [ORR24W]) with an improved safety

profile compared to lenvatinib 18 mg in combination with everolimus 5 mg (based on treatment-emergent intolerable Grade 2, or any >= Grade 3 adverse events (AEs) in the first 24 weeks after randomization).

Secondary Objectives
• To assess progression-free survival (PFS).
• To assess ORR.
• To determine the tolerability and safety profile of lenvatinib in combination with everolimus.
• To assess the proportion of subjects who discontinued treatment due to toxicity.
• To assess time to treatment failure due to toxicity.
• To assess pharmacokinetic (PK) profiles of lenvatinib and everolimus during combination therapy and to assess PK and pharmacodynamic (PD) drug-drug interactions.
• To evaluate overall survival (OS).
• To evaluate the impact of disease and treatment on patients' Health-Related Quality of Life (HRQoL) as assessed by using the Functional Assessment of Cancer Therapy Kidney Symptom Index-Disease-Related Symptoms (FKSI-DRS), the European Organization for the Research and Treatment of Cancer (EORTC) QLQ-C30 and the European Quality of Life (EuroQol) EQ-5D-3L.
• To evaluate the PFS after next line of treatment (PFS2).

Exploratory Objectives
• To explore tumor response parameters (ORR24W, ORR, PFS) based on blinded independent imaging review (IIR) for efficacy assessment.

Study design

multicenter, randomized, open-label study

Intervention

The patient will be assigned to one of the two treatment groups and will receive a starting dose of either:
• Group A lenvatinib 18mg and everolimus 5mg orally once daily or
• Group B lenvatinib 14mg and everolimus 5mg orally once daily.

The 14 mg starting dose will be escalated to 18 mg if no Grade 2 (intolerable) or any >= Grade 3 treatment-emergent adverse events (TEAEs) that require dose reduction are observed in the first cycle (4 weeks) of treatment. If Grade 2 (intolerable) or Grade 3 or 4 TEAEs are observed, the lenvatinib dose will be reduced.

Study burden and risks

Very Common Side Effects of lenvatinib:
high or low blood pressure, loss of appetite or weight loss, feeling sick and being sick, constipation, diarrhoea, abdominal pain, indigestion, feeling very tired or weak, dry, sore, or inflamed mouth or throat, high levels of protein in the urine, hoarse voice, headache, hand-foot syndrome, joint pains, cough, low level of platelets in the blood which may lead to bruising, musculoskeletal, muscle, limb or back pain, swelling of the legs, underactive thyroid and change in blood test result for thyroid stimulating hormone (high), rash, feeling dizzy, bleeding (most commonly nose bleeds, but may include bleeding from other sites such as blood in the urine, bruising, bleeding from the gums, coughing up blood), odd taste sensation, trouble sleeping, hair loss, urinary infections, changes in blood test results for potassium levels (low) and calcium levels (low).

Very Common Side Effects of everolimus:
Decrease in the number of blood cells produced in the bone marrow, Infections, Increased blood glucose, increased cholesterol, Feeling weak or tired, Loss of appetite, weight loss, Abnormal taste, Stomatitis (sore mouth / tongue and ulceration), Cough, Nose bleeds, Skin rash, itching sensation, Peripheral edema (swelling of arms and/or legs due to fluid retention), Headache, Upset stomach including feeling sick or diarrhoea.

The combination of lenvatinib with everolimus has been approved for use. This study will evaluate an alternative dosing regimen to determine whether this regimen provides comparable efficacy but has a better safety profile.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Histological or cytological confirmation of predominant clear cell RCC (original tissue diagnosis of RCC is acceptable)., 2. Documented evidence of advanced RCC., 3. One prior disease progression episode on or after VEGF-targeted treatment (for example, but not limited to, sunitinib, sorafenib, pazopanib, cabozantinib, bevacizumab, axitinib, vatalanib, AV951/tivozanib) administered for the treatment of RCC. Prior PD-1/PD-L1 treatment in addition to 1 prior VEGF-targeted treatment is allowed., 4. At least 1 measurable target lesion according to RECIST 1.1 meeting the following criteria:, Lymph node (LN) lesion that measures at least 1 dimension as >=1.5 cm in the short axis Non-nodal lesion that measures >=1.0 cm in the longest diameter, The lesion is suitable for repeat measurement using computerized tomography/magnetic resonance imaging (CT/MRI). Lesions that have had external beam radiotherapy (EBRT) or locoregional therapy must show radiographic evidence of disease progression based on RECIST 1.1 to be deemed a target lesion., 5. Male or female subjects age >=18 years (or any age >18 years if that age is considered to be an adult per the local jurisdiction) at the time of informed consent., 6. Karnofsky Performance Status (KPS) of >=70., 7. Adequately controlled blood pressure (BP) with or without antihypertensive medications, defined as BP <=150/90 mmHg at Screening and no change in antihypertensive medications within 1 week before Cycle 1/Day 1., 8. Adequate renal function defined as calculated creatinine clearance >=30 mL/min per the Cockcroft and Gault formula (Appendix 1)., 9. Adequate bone marrow function defined by:, Absolute neutrophil count (ANC) >=1500/mm3 (>=1.5 x 109/L) Platelets >=100,000/mm3(>=100 x 109/L) Hemoglobin >=9 g/dL., 10. Adequate blood coagulation function defined by International Normalized Ratio (INR) <=1.5 (except for subjects on warfarin therapy where INR must be <=3.0 prior to randomization)., 11. Adequate liver function defined by:, Total bilirubin <=1.5 times the ULN except for unconjugated hyperbilirubinemia of Gilbert*s syndrome., Alkaline phosphatase (ALP), alanine aminotransferase (ALT), and aspartate aminotransferase (AST)

<=3×ULN (in the case of liver metastases <=5×ULN). Subjects with bone metastases with ALP values greater than 3 times can be included., 12. Subject must voluntarily agree to provide written informed consent., 13. Subject must be willing and able to comply with all aspects of the protocol.

Exclusion criteria

1. More than 1 prior VEGF-targeted treatment for advanced RCC., 2. Subjects with Central Nervous System (CNS) metastases are not eligible, unless they have completed local therapy for at least 4 weeks and have discontinued the use of corticosteroids for this indication or are on a tapering regimen of corticosteroids (defined as <=10 mg prednisolone equivalent) before starting treatment in this study. Any signs (eg, radiologic) or symptoms of brain metastases must be stable for at least 4 weeks before starting study treatment., 3. Active malignancy (except for RCC or definitively treated basal or squamous cell carcinoma of the skin, or carcinoma in-situ of the cervix or bladder) within the past 24 months., 4. Any anti-cancer treatment (except for radiation therapy, see exclusion #5) within 21 days, or any investigational agent within 30 days prior to the first dose of study drug; subjects should have recovered from any toxicity related to previous anti-cancer treatment to CTC grade 0 or 1., 5. Prior radiation therapy within 21 days prior to start of study treatment with the exception of palliative radiotherapy to bone lesions, which is allowed if completed 2 weeks prior to study treatment start., 6. Known intolerance to study drug (or any of the excipients) and/or known hypersensitivity to rapamycins (eg, sirolimus, everolimus, temsirolimus) or any of the excipients., 7. Subjects with proteinuria > 1 + on urinalysis will undergo 24-h urine collection for quantitative assessment of proteinuria. Subjects with urine protein >=1 g/24 h will be ineligible., 8. Fasting total cholesterol > 300 mg/dL (or > 7.75 mmol/L) and/or fasting triglycerides level > 2.5 x ULN. NOTE: these subjects can be included after initiation or adjustment of lipid-lowering medication., 9. Uncontrolled diabetes as defined by fasting glucose > 1.5 times the ULN. NOTE: these subjects can be included after initiation or adjustment of glucose-lowering medication., 10. Prolongation of QTc interval to > 480 ms., 11. Subjects who have not recovered adequately from any toxicity and/or complications from major surgery prior to starting therapy., 12. Gastrointestinal malabsorption, gastrointestinal anastomosis, or any other condition that might affect the absorption of lenvatinib or everolimus., 13. Bleeding or thrombotic disorders or subjects at risk for severe hemorrhage. The degree of tumor invasion/infiltration of major blood vessels (eg, carotid artery) should be considered because of the potential risk of severe hemorrhage associated with tumor shrinkage/necrosis following lenvatinib therapy., 14. Clinically significant hemoptysis or tumor bleeding within 2 weeks prior to the first dose of study drug., 15. Significant cardiovascular impairment within 6 months prior to the first dose of study drug; history of congestive heart failure greater than New York Heart

Association (NYHA) Class II,unstable angina, myocardial infarction or stroke, cardiac arrhythmia associated with significant cardiovascular impairment, or left ventricular ejection fraction (LVEF) below the institutional normal range as determined by screening multigated acquisition (MUGA) scan or echocardiogram., 16. Active infection (any infection requiring systemic treatment)., 17.Any medical or other condition that in the opinion of the investigator(s) would preclude the subject*s participation in a clinical study., 18. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin [ß-hCG] (or human chorionic gonadotropin [hCG]) test with a minimum sensitivity of 25 IU/L or equivalent units of ß-hCG [or hCG]). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug., 19. Females of childbearing potential* who:, do not agree to use a highly effective method of contraception for the entire study period and for up to 8 weeks after study drug discontinuation, ie:, - total abstinence (if it is their preferred and usual lifestyle), - an intrauterine device (IUD) or hormone releasing system (IUS), - a contraceptive implant, - an oral contraceptive** (with additional barrier method), OR, do not have a vasectomized partner with confirmed azoospermia., For sites outside of the EU, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie double barrier methods of contraception, such as condom plus diaphragm or cervical/vault cap with spermicide.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed

Start date (anticipated):	08-04-2018
Enrollment:	13
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Afinitor
Generic name:	everolimus
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Kisplyx
Generic name:	lenvatinib
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	09-05-2017
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-07-2017
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	05-12-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	19-12-2017
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	23-02-2018
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	19-03-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	01-08-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	13-08-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-10-2018
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-01-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	23-01-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-02-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	05-03-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	03-04-2019
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	09-09-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-09-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-10-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	14-10-2019
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	26-02-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	03-03-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2016-002778-11-NL
CCMO	NL60657.028.17